#3640 INFUSION OF "OFF-THE-SHELF" THIRD PARTY EX VIVO EXPANDED CORD BLOOD PROGENITOR CELLS AS SUPPORTIVE CARE FOLLOWING CLOFARABINE WITH HIGH DOSE CYTARABINE AND GRANULOCYTE COLONY-STIMULATING FACTOR PRIMING FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

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BACKGROUND

Regardless of patient age, prolonged neutropenia and infectious complications are common side effects of AML induction and salvage chemotherapy, requiring intensive supportive care and contributing to treatment failure.

In a cohort of 50 patients, Becker et al at the Fred Hutchinson Cancer Research Center have reported on the use of clofarabine and high dose ara-c, in combination with G-CSF (GCLAC) in a Phase I/II trial for the treatment of relapsed/ refractory AML (Becker et al). GCLAC is profoundly immunosuppressive and myelosuppressive, with periods of prolonged neutropenia post-GCLAC ranging from 17 to 35 days (median time to ANC >500 is 21 days) in this cohort. Infection was the most frequent adverse event, with ≥ grade 3 bacterial and fungal infections seen in 40% of patients (including 1st and ≥ 2nd salvage patients).

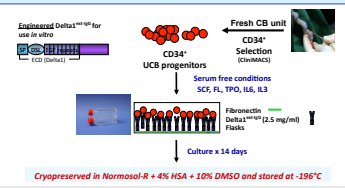
Previously, we have demonstrated that the absolute number of repopulating cord blood (CB) hematopoietic stem/progenitor cells (HSPC) can be increased by culture with Notch ligand; recent data from a Phase I double CB transplant trial utilizing ex vivo expanded CB HSPC has suggested more rapid neutrophil recovery (Delaney et al, Nat Med).

We now herein report the preliminary results of a Phase I safety trial investigating the use of GCLAC plus infusion of off-the-shelf expanded and cryopreserved CB HSPC for patients with AML.

OBJECTIVE

We hypothesize that this expanded cell product, which is devoid of T cells, could be cryopreserved and then infused as an off-the-shelf non-HLA matched product to provide rapid but temporary donor myeloid engraftment and might also facilitate autologous hematopoietic recovery following AML therapy, thus reducing the infectious complications associated with therapy.

NOTCH-MEDIATED EXPANSION SYSTEM



INCLUSION CRITERIA

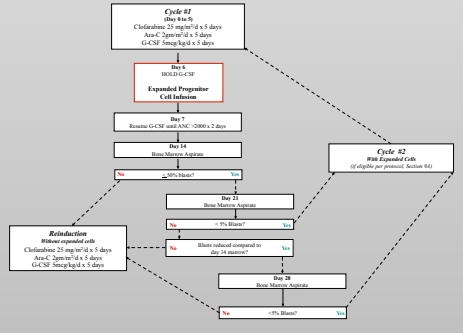
Three Cohorts (10-15 patients each)

Cohort A: Diagnosis of acute myeloid leukemia by WHO criteria, **either relapsed or refractory**. APL [Acute promyelocytic leukemia with t(15;17)(q22;q12) and variants] will be eligible only after failure of a regimen containing arsenic trioxide. Patients in this cohort must have had an initial remission duration of < 1 year and not have received any prior salvage chemotherapy.

Cohort B: Untreated AML patients, excluding those with favorable cytogenetic or molecular abnormalities per the European LeukemiaNet recommendations.

Cohort C: Untreated AML patients, including those with favorable cytogenetics or molecular abnormalities per the European LeukemiaNet recommendations.

PLAN OF TREATMENT



RESULTS

		Demographics			Cell Dose	Neutrophils	Infections	Chimerism (7 days post infusion)					
		Gender	Age (yrs)	Weight (kg)	CD34 x 10^6/kg	ANC >500 (days)	Blood infections unless noted	CD33	CD14	CD56	CD3	unsorted	BM Chim
COHORT A (relapsed or primary refractory* patients)													
Patient 1	cycle 1	M	55	126	4.4	22	Roseomonas mucosa Mycobacterium, Coag neg staph	0	0	0	0	0	0
	cycle 2				**3.8**	**59**	Aspergillus (presumed)	**100**	**100**	**0**	**0**	**25**	**11**
Patient 2*	cycle 1	F	59	70	5.4	18	NONE	0	0	0	0	0	0
	cycle 2				**9.7**	**19**	NONE	**85**	**100**	**0**	**0**	**30**	**3**
Patient 3	cycle 1	F	58	78	7.3	27	Strep Mitus	0	0	0	0	0	0
Patient 4*	cycle 1	F	59	94	5.7	19	NONE	0	0	0	0	0	0
	cycle 2				**3.8**	**18**	Coag neg Staph	**0**	**93**	**0**	**0**	**5**	**0**
Patient 5	cycle 1	M	57	81	6.8	18	NONE	n/d	n/d	n/d	n/d	0	Blasts
Patient 6	cycle 1	F	40	64	4.4	Blast recovery	NONE	0	0	0	0	0	Blasts
Patient 7	cycle 1	M	45	95	5.9	Blast recovery	Coag Neg Staph VRE	0	0	0	0	0	Blasts
Patient 8	**cycle 1**	F	56	70	4.4	**24**	alpha hemolytic strep E. Coli (urine)	**43**	**QNS**	**QNS**	**0**	**23**	**22**
Patient 9*	cycle 1	M	51	76	10.7	Blast recovery	NONE	QNS	0	0	0	0	Blasts
Patient 10	cycle 1	M	55	87	8.9	19	NONE	QNS	QNS	0	0	0	0
Median (Range)			**56 (40-59)**	**79 (64-126)**	**5.6 (3.7-10.7)**	**19 (18-59)**							
COHORT B (de novo, excluding favorable cyto or molecular abnormalities)													
Patient 11	cycle 1	M	38	85	6.4	23	NONE	QNS	QNS	0	0	0	0
	cycle 2					**19**	NONE	**98**	**96**	**0**	**0**	**4**	**0**
Patient 12	cycle 1	M	56	75	6.0	19	NONE	0	0	0	0	0	0
Patient 13	cycle 1	M	49	138	8.1	19	NONE	0	0	0	0	0	0
	cycle 2					20	NONE	0	0	0	0	0	0
Patient 14	**cycle 1**	F	33	102	**2.4**	**18**	NONE	**91**	**n/a**	**0**	**0**	**23**	**0**
	cycle 2					20	NONE	0	0	0	0	0	0
Patient 15	**cycle 1**	M	66	78	**5.8**	**30**	NONE	**56**	**100**	**4**	**2**	**37**	**0**
Median (Range)			**48(33-66)**	**85 (75-138)**	**5.9 (2.4-8.1)**	**19.5 (18-30)**							

CONCLUSIONS

- Infusion of non-HLA matched ex vivo expanded and cryopreserved CB HSPC following GCLAC therapy in patients with relapsed/refractory or de novo AML is safe with no infusional toxicities from the expanded cells or adverse events attributed to the expanded cell product.
- Transient contribution to myeloid recovery from the non-HLA matched donor product was observed in 4 out of 7 evaluable relapsed/refractory patients and 3 out of 5 de novo patients.
- The median time to reach an ANC >500 was 19 and 19.5 days in Cohorts A and B, respectively.
- Infections were observed in 6 of the 15 patients, however no deaths due to infection have been observed to date.

REFERENCES

Becker PS, et al. *Clofarabine with high dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming for relapsed and refractory acute myeloid leukaemia*. Br J Haemotol, 2011 Oct;155(2):182-9.

Delaney C, et al. *Notch-mediated Expansion of Human Cord Blood Progenitor Cells Capable of Rapid Myeloid Reconstitution*. Nat Med 2010 Feb; 16(2):232-6.

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